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Mitigation of Inflammation-Induced Mood Dysregulation by Long-Chain Omega-3 Fatty Acids

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Abstract

Although evidence suggests that chronic elevations in immune-inflammatory signaling can precipitate mood symptoms in a subset of individuals, associated risk and resilience mechanisms remain poorly understood. Long-chain omega-3 (LCn-3) fatty acids, including eicosapentaenic acid (EPA) and docosahexaenoic acid (DHA), have anti-inflammatory and inflammation-resolving properties which maintain immune-inflammatory signaling homeostasis. Cross-sectional evidence suggests that the mood disorders major depressive disorder and bipolar disorder are associated with low EPA and/or DHA biostatus, elevations in the LCn-6/LCn-3 fatty acid ratio, and elevated levels of pro-inflammatory eicosanoids, cytokines, and acute-phase proteins. Medications that are effective for reducing depressive symptoms or stabilizing manic-depressive oscillations may act in part by down-regulating immune-inflammatory signaling and are augmented by anti-inflammatory medications. Recent prospective longitudinal evidence suggests that elevations in the LCn-6/LCn-3 fatty acid ratio are a modifiable risk factor for the development of mood symptoms, including depression and irritability, in response to immune-inflammatory signaling. Together these data suggest that increasing LCn-3 fatty acid intake and biostatus represents a feasible strategy to mitigate the negative impact of elevated immune-inflammatory signaling on mood stability.

Keywords

Omega-3 fatty acids; Docosahexaenoic acid (DHA); Arachidonic acid; Cytokines; Inflammation; Mood; Depression; Bipolar disorder

INTRODUCTION

Major mood disorders including major depressive disorder (MDD) and bipolar disorder are characterized by severe and recurrent emotional homeostasis dysregulation. Bipolar disorder is typically characterized by recurrent episodes of depression and mania, and untreated patients typically exhibit progressive increases in the frequency and severity of mood episodes over time. The initial onset of mania, and by definition bipolar I disorder, and MDD most frequently occurs during childhood and adolescence [1,2], and the initial onset

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of mania is frequently preceded by several years of syndromal or subsyndromal MDD and/or subsyndromal manic symptoms including anger and irritability [3]. Outcomes data indicate that MDD and bipolar disorder are associated with significant psychosocial morbidity and excess premature mortality primarily due to suicide [4,5]. Therefore, mood disorders represent a significant public health problem and developing a better understanding of risk and resilience mechanisms will be required to guide new treatment and prevention strategies.

Major advances in the treatment and prevention of mood disorders will be accelerated by the identification of pathogenic mechanisms conferring vulnerability as well as modifiable resilience factors. Over that past twenty years a body of translational evidence has implicated elevations in immune-inflammatory signaling in the pathophysiology of mood disorders [6]. Evidence from prospective longitudinal studies further suggest that elevated immune-inflammatory signaling can trigger severe mood dysregulation in a subset of non-psychiatric patients [7], though associated risk and resilience mechanisms are not known. In parallel, cross-national and cross-sectional epidemiological studies, case-control studies, and controlled prospective supplementation trials have implicated dietary polyunsaturated fatty acids (PUFA) in the maintenance of immune-inflammatory signaling homeostasis [8] as well as the pathophysiology of mood disorders [9]. This article will provide a brief overview of evidence implicating PUFA intake/status as a moderator of elevated immune-inflammatory signaling effects on mood.

PUFA REGULATION OF IMMUNE-INFLAMMATORY SIGNALING

The PUFA family consists of omega-6 and omega-3 fatty acids which are considered 'essential' because mammals are completely dependent on dietary sources to procure and maintain adequate tissue concentrations. Principal dietary sources of the short-chain omega-3 fatty acid precursor α -linolenic acid (ALA, 18:3 n -3) include flaxseed, linseed, canola, soy, and perilla oils. Primary dietary sources of the short-chain omega-6 fatty acid precursor linoleic acid (LA, 18:2 n -6) include safflower, soy, and corn oils. The biosynthesis of long-chain omega-3 (LC n -3) fatty acids, including eicosapentaenoic acid (EPA, 20:5 n -3) and docosahexaenoic acid (DHA, 22:6 n -3), and LC n -6 fatty acids, including arachidonic acid (AA, 20:4 n -6), from their short-chain precursors require a series of common and competitive microsomal desaturation and elongation reactions [10]. Nevertheless, supplementation studies suggest that ALA $\rightarrow$ DHA and LA $\rightarrow$ AA biosynthesis is extremely limited in healthy adult human subjects and that preformed LC-PUFAs are significantly more efficient for increasing LC-PUFA biostatus [11–14].

Translational evidence suggests that immune-inflammatory signaling is inversely regulated by the LC n -6 fatty acid AA and LC n -3 fatty acids EPA and DHA. Phospholipid-bound AA is mobilized via calcium-dependent cytosolic isoform of phospholipase A₂ (cPLA₂) and unesterified AA serves as a substrate for cyclooxygenase (COX)-mediated biosynthesis of prostoglandins (i.e., PGE₂), thromboxanes, and prostacyclins, as well as lipoxygenase-mediated biosynthesis of leukotrienes. Eicosanoids including PGE₂ can stimulate the biosynthesis of down-stream pro-inflammatory cytokines including interleukin-6 (IL-6) at the level of transcription [15–17] which in turn stimulate biosynthesis of acute phase

proteins including C-reactive protein (CRP)[18,19]. In contrast, the LCn-3 fatty acids EPA and DHA are predominantly anti-inflammatory and EPA competes with AA for metabolism by COX enzymes [20] and metabolites of DHA and EPA (i.e., D- and E-series resolvins) have potent inflammation-resolving properties [21,22]. These and other biochemical data support the notion that the balance between LCn-6 and LCn-3 fatty acids plays a key role in maintaining immune-inflammatory signaling homeostasis.

Consistent with these biochemical observations rodent studies have found that dietary-induced reductions in LCn-3 fatty acid biostatus, and associated elevations in the LCn-6/LCn-3 fatty acid ratio, are associated with constitutive increases IL-6, TNF α , and CRP concentrations in rat plasma [23], and augmented lipopolysaccharide (LPS)-stimulated elevations in rodent plasma IL-6 levels [24]. Moreover, dietary-induced elevations in the LCn-6/LCn-3 fatty acid ratio are associated with reductions calcium-independent iPLA $_2$, which mobilizes DHA, and elevations in cPLA $_2$ and COX-2 expression and activity in rat brain [25]. Central immune-inflammatory processes are mediated in part by microglia and LCn-3 fatty acids inhibit constitutive and LPS-induced microglial activation, pro-inflammatory cytokine production, and COX expression [26–30]. Furthermore, membrane EPA and DHA levels in of circulating peripheral blood mononuclear cells, including lymphocytes, leukocytes, and neutrophils, are positively correlated with LCn-3 fatty acid intake [31] and in general negatively regulate immune-inflammatory signaling [8]. Accordingly, cross-sectional studies have observed an inverse association between dietary or blood LCn-3 fatty acid levels and pro-inflammatory cytokine and CRP levels in healthy populations [32–38]. Together, these translational data suggest that reductions in LCn-3 fatty acid biostatus, and associated elevations in the LCn-6/LCn-3 fatty acid ratio, increase systemic immune-inflammatory signaling activity.

PUFA IMBALANCE IN MOOD DISORDERS

Several different lines of evidence have implicated a PUFA imbalance in the pathophysiology of mood disorders. First, cross-national epidemiological surveys have found that greater habitual dietary intake of fish/seafood (i.e., major dietary sources of LCn-3 fatty acids) is associated with reduced lifetime prevalence rates of MDD [39,40], postpartum depression [41], and bipolar disorder [42]. Second, cross-sectional population studies have observed an inverse association between fish intake and risk for developing depression [43–46]. Third, erythrocyte (red blood cell) membrane EPA and DHA composition is highly correlated with habitual LCn-3 fatty acid intake [47,48], and case-controls studies have observed reduced erythrocyte EPA and/or DHA levels, and associated elevations in the LCn-6/LCn-3 fatty acid ratio, in patients with MDD [49] and bipolar disorder [50]. Significant DHA deficits have also been observed in postmortem prefrontal cortex of patients with MDD [51] and bipolar disorder [52]. Fourth, independent meta-analyses of controlled LCn-3 fatty acid supplementation trials have observed a significant advantage over placebo for the treatment of syndromal depressive symptoms in patients with MDD [53,54] or bipolar disorder [55]. Taken collectively, this body of evidence supports a link between mood dysregulation and low habitual dietary LCn-3 fatty acid intake and biostatus.

ELEVATED IMMUNE-INFLAMMATORY SIGNALING IN MOOD DISORDERS

Several cross-sectional studies have investigated immune-inflammatory markers in patients with established mood disorders. Early studies observed elevated PGE₂ levels in the saliva, plasma, and cerebrospinal fluid of MDD patients which were positively associated with depression symptom severity [56–60]. A meta-analysis of 24 case-control studies observed significantly higher blood concentrations of IL-6 and TNF α in MDD patients [61]. A case-control study also observed higher levels of the acute phase protein CRP in MDD patients [62]. Greater IL-6, IL-6R, IL-2R, IL-1 β , TNF α and/or CRP levels have also been observed in bipolar patients during depressive and acute manic episodes compared with healthy controls [63]. Moreover, a postmortem brain study [64] and a recent positron emission tomography study [65] provide evidence for elevated microglia activation in patients with mood disorders. Therefore, evidence from cross-sectional studies support an association between mood dysregulation and elevated peripheral and central immune-inflammatory signaling activity.

Additional support is provided by findings that medications that are efficacious for the treatment of mood symptoms down-regulate immune-inflammatory signaling. For example, different antidepressant medications suppress LPS-induced production of pro-inflammatory cytokines including TNF α and IL-6 [66], and reduce the development of cytokine-induced depressive-like behavior [67]. Although clinical studies have not consistently observed reductions serum pro-inflammatory cytokine levels in MDD patients following treatment with antidepressant medications [68], adjunctive treatment with the selective COX-2 inhibitor celecoxib [69] or the COX-1 inhibitor aspirin [70] augment antidepressant efficacy. Mood-stabilizer medications including lithium chloride are used for the prophylactic stabilization of mood oscillations in bipolar patients, and extant clinical evidence suggests they suppress peripheral pro-inflammatory cytokine production [71,72]. Moreover, a common mechanism of action of different mood-stabilizer medications in rat brain is down-regulation of cPLA₂-mediated AA mobilization from phospholipids and associated reductions in COX-2-mediated PGE₂ production [73].

There are several plausible mechanisms by which elevated immune-inflammatory signaling may contribute to mood dysregulation (Figure 1). First, elevated central serotonin (5-HT) turnover has been implicated in the pathophysiology and treatment of MDD [74,75], and preclinical studies have found that peripheral administration of IL-6 significantly increases serotonin turnover in rat brain [76]. Moreover, central levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) are elevated following peripheral administration of IL-1 β or TNF α [77], and chronic peripheral administration of IFN- α increase 5-HT turnover in rat frontal cortex [78]. Moreover, depressive symptoms during interferon- α (IFN- α) treatment are associated with CSF 5-HIAA concentrations which are a significant predictor of emergent depressive symptoms [79]. Second, several independent findings have implicated hypothalamic-pituitary-adrenal (HPA) axis dysregulation in the pathophysiology of mood disorders [80], and emerging preclinical evidence suggests that pro-inflammatory cytokines increase HPA axis activity and reactivity [81,82]. Third, elevated immune-inflammatory signaling is associated with white matter pathology [83] and reductions in myelin-associated gene expression [84,85] and myelin staining [86] are observed in the

postmortem brain of bipolar and MDD patients. Diffusion tensor imaging studies have also revealed deficits in central white matter structural integrity in patients with bipolar disorder [87] or MDD [88]. Fourth, emerging evidence from preclinical [89] and clinical [90] imaging studies suggest that elevated immune-inflammatory signaling is associated with reductions in gray matter volumes in limbic structures which are reduced in patients with mood disorders [91].

PUFA, IMMUNE-INFLAMMATORY SIGNALING, & MOOD DYSREGULATION

While parallel cross-sectional evidence supports a potential link between elevations in the LCn-6/LCn-3 fatty acid ratio and elevated immune-inflammatory signaling activity in mood disorders, recent prospective studies provide evidence for a direct link with mood dysregulation. In a within-subject prospective study of 138 subjects lower baseline plasma DHA levels, and a higher AA/EPA+DHA ratio, were associated with increased risk for developing a major depressive episode during treatment with the pro-inflammatory cytokine IFN- α [92]. The latter study also found that a higher baseline AA/EPA+DHA ratio was associated with greater treatment-induced increases plasma IL-6 levels. These prospective data support another study finding that lower erythrocyte DHA levels were associated with increased risk for developing a major depressive episode during IFN- α treatment [93]. A separate prospective study of 82 subjects found that a higher baseline AA/EPA+DHA ratio was positively associated with manic-like symptoms including anger and irritability during IFN- α treatment [94]. A controlled supplementation trial found that pretreatment with EPA alone, which increased both erythrocyte EPA and DHA levels, but not DHA alone decreased the incidence of depression during IFN- α treatment [95]. Therefore, prospective evidence provides strong support for a mitigating effect of LCn-3 fatty acid status in mood dysregulation in response to elevated immune-inflammatory signaling activity.

SUMMARY AND CONCLUSIONS

There is now compelling translational evidence implicating elevated systemic immune-inflammatory signaling activity in the pathophysiology of mood disorders. Medications that are effective for reducing depressive symptoms or stabilizing manic-depressive oscillations may act in part by down-regulating immune-inflammatory signaling and are augmented by anti-inflammatory medications. Parallel studies have demonstrated that LCn-3 fatty acids have anti-inflammatory, inflammation-resolving, and neuroprotective properties, and that major mood disorders are associated with peripheral and central LCn-3 fatty acids deficits and associated elevations in the LCn-6/LCn-3 fatty acid ratio. Recent prospective data suggest that elevations in the LCn-6/LCn-3 fatty acid ratio increase vulnerability to inflammation-induced mood dysregulation which can be mitigated by increasing LCn-3 fatty acid status. While that latter evidence is based on exogenous administration of IFN- α , other stimuli including viral infections [96,97] and allergies [98–100] represent naturalistic triggers of immune-inflammation activity. Plausible mechanisms by which elevated immune-inflammatory signaling may contribute to mood dysregulation including alterations in serotonin turnover and metabolism, HPA axis dysregulation, and white and gray matter pathology. Taken collectively, this body of evidence supports a pathogenic link between low LCn-3 fatty acid intake and status, associated elevations in the LCn-6/LCn-3 fatty acid ratio,

and vulnerability to inflammation-induced mood dysregulation. Increasing LCn-3 fatty acid intake may therefore represent a feasible strategy to protect against inflammation-induced mood dysregulation and warrants additional investigation.

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Key teaching points

- Long-chain omega-3 (LCn-3) fatty acids have anti-inflammatory and inflammation-resolving properties.
- Major mood disorders are associated with both LCn-3 fatty acids deficiency and elevated immune-inflammatory signaling.
- Prospective evidence suggests that low LCn-3 fatty acid biostatus increases risk for developing inflammation-induced mood dysregulation.
- Taken collectively, this evidence suggests that increasing LCn-3 fatty acid intake and biostatus represents a promising strategy to mitigate the detrimental effects of elevated immune-inflammatory signaling on mood.

Figure 1.

Diagram illustrating the proposed link between dietary PUFA intake and metabolism, elevations in the LCn-6/LCn-3 fatty acid ratio, elevated immune-inflammatory signaling, and mood dysregulation. Elevated immune-inflammatory signaling may be triggered by IFN- α , as well as other naturalistic stimuli including viral or bacterial infections and allergies, and is down-regulated by anti-inflammatory medications including aspirin and celecoxib and mood-stabilizers (i.e., lithium) and potentially antidepressants. Elevated immune-inflammatory signaling adversely impacts serotonin turnover and metabolism and HPA axis activity, and is associated with white and gray matter pathology, which together precipitate mood dysregulation.